UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,343	10/18/2000	C. Alexander Turner JR.	LEX-0070-USA	3960

24231 7590 05/18/2004

LEXICON GENETICS INCORPORATED
8800 TECHNOLOGY FOREST PLACE
THE WOODLANDS, TX 77381-1160

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

mailed 5-18-04

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/691,343
Filing Date: October 18, 2000
Appellant(s): TURNER *ET AL.*

David W. Hibler
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed on 19 February 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The Appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 4-11 stand or fall together because Appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,194,596	Tischer *et al.*	03-1993

Skolnick *et al.*, 2000, Trends in Biotechnology Vol. 18/1:34-39.

Yan *et al.*, 2000, Science Vol. 290:523-527.

Wells, 1990, Biochemistry Vol. 29:8509-8517.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections—35 U.S.C. § 101

Claims 4-11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to isolated polynucleotides (SEQ ID NO:6) and isolated polynucleotides encoding polypeptides (SEQ ID NO:7) of novel human proteins (NHPs). The specification states that NHPs share structural motifs typical of human secreted proteins (page 2, lines 8-9). NHPs share structural similarity with animal chordins, NEL protein, and thrombospondin (page 2, lines 13-24). The specification states that when secreted, the NHPs typically exert physiological effects by interacting with receptors to produce a biological effect. Interfering with the binding of a NHP product to its cognate receptor affects NHP-mediated processes (page 4, lines 20-30).

The instant specification, however, never actually demonstrates that the claimed invention possesses any biological activity. The specification does not disclose any information regarding ligands or functional characteristics/mechanisms of action of NHPs. The specification fails to disclose the physiological effects that occur when NHP binds its receptor. The specification does not disclose a receptor for NHP. Ligand-binding experiments and/or second-messenger assays were never executed to conclusively discern a function for NHP. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). The assertion that NHPs have biological activities similar to known proteins which are cited in the instant specification cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer *et al.* (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells. This is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). Yan *et al.* (Science 2000) establishes that a change in two amino acids in an epithelial

morphogen regulates binding to two distinct receptors. In addition, polynucleotides are known in the art to encode polypeptides, yet the polypeptides have no known function.

The specification asserts several utilities, however the claimed invention lacks specific and substantial utility. Some of the asserted utilities include methods to screen for agonists and/or antagonists of NHP, using probes to isolate other cDNAs, screening for binding proteins and making antibodies. Agonist/antagonist assays are performed for any receptor-ligand pair when the physiological role of each is unknown. Antibodies can be made to any protein. A probe is a general utility that would be applicable to the broad class of the invention. A specific utility amounts to more than a starting point for further research and investigation. It does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be.

The specification states that a variety of methods can be employed for the diagnostic and prognostic evaluation of disorders related to NHP function. The specification establishes no connection between any disease/condition. For example is NHP mutated, deleted or overexpressed? There is no correlation to the predisposition of a particular disease and the claimed invention. The specification does not disclose any working examples demonstrating that the instant invention was used to treat any disease. Further experimentation is required before this asserted utility is substantial. Indeed, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product,

if the claimed DNA had a specific and substantial utility such as it hybridizes near a disease-associated gene or it has a gene regulating activity. The specification, however, fails to disclose that the DNA of the instant application can be linked to a specific disease or gene regulating activity.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed invention.

Claim Rejections—35 U.S.C. § 112, First Paragraph (Enablement)

Claims 4-11 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if a specific and substantial or well established utility were identified, the specification would still not be enabling for polynucleotides comprising fragments (claims 4, 7 and 8). It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases (Wells, 1990, Biochemistry 29:8509-8517). The disclosure provides no guidance as to which regions of the sequence would be tolerant of modification and which would not, and it provides no working

example of any variant sequence which would be within the claims. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections—35 U.S.C. § 112, First Paragraph (Written Description)

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 4 is drawn to an isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP gene described in SEQ ID NO:6.

The specification discloses SEQ ID NO:6 which corresponds to the DNA encoding protein NHP. Claim 4 is directed to encompass gene sequences from other species, mutated sequences, allelic variants, splice variants and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Claim 4 recites a genus of nucleic acid molecules comprising at least 24 contiguous nucleotides of SEQ ID NO:6. Thus, it encompasses virtually any random sequence of any length as long as it has a stretch of at least 24 consecutive nucleotides that is the same as SEQ ID NO:6.

The instant disclosure of a single species of nucleic acid of SEQ ID NO:6 does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of nucleic acid molecules. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated

and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed nucleic acid molecules as being identical to those instantly claimed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "Appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:6, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an Appellant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Due to the breadth of the claim genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus. Therefore, only SEQ ID NO:6 but not the full breadth of the claims meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Appellant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision.

(11) Response to Argument

A. Do claims 4-11 lack a Patentable Utility?

Beginning at page 4 of the Brief, Appellant argues that the present nucleic acid sequences have utility in diagnostic assays such as forensic analysis, as described in the specification as originally filed. Appellant states that the presently claimed sequence defines a coding single nucleotide polymorphism specifically, an A/T polymorphism at position 598 of SEQ ID NO:6, which can lead to an isoleucine or valine residue at amino acid position 200 of SEQ ID NO:7. Appellant states, "as polymorphisms such as this are the basis for forensic analysis, which is undoubtedly a real world utility, the presently claimed sequence must in itself be useful".

At page 5 of the Brief, Appellant submits that in the Final Action, the Examiner questioned this asserted utility, stating it does not mean that the change in amino acid will affect activity or cause a disease or condition. Appellant states that the Examiner reiterates this position in the Advisory Action, stating that a way of identifying a population of people which carry a particular polymorphism, wherein the polymorphism itself does not cause a disease or condition lacks a substantial utility and fails to have a real world use.

Appellant maintains that naturally occurring genetic polymorphisms such as that described in the present specification are both the basis of and critical to, forensic genetic analysis intended to resolve issues of, for example, identity or paternity. Forensic analysis based on identified polymorphisms such as that identified by Appellants is used to positively identify or rule out suspects in many

criminal cases, and in identifying human remains. Appellant states these are all well known and generally accepted uses of identified polymorphisms such as the polymorphism identified by Appellants. Without such identified polymorphisms, the skilled artisan would not be able to carry out such forensic or paternal analyses. Thus, the Examiner's argument in no way supports the allegation that the presently claimed sequence lacks a patentable utility.

On page 6 of the Brief, Appellant argues that forensic analysis does not require any information at all about the ultimate biological function of the encoded protein, or require that the mutation cause a disease or condition. Appellant states that using the polymorphic marker; the skilled artisan can distinguish members of a population from one another without any additional research. Appellant maintains that the asserted forensic utility is specific because it cannot be applied to just any polynucleotide and that the basis for the forensic analysis is the fact that such polymorphic markers are not present in all other nucleic acids, but in fact specific and unique to only a subset of the population.

The Examiner understands that Appellant is arguing the utility of the instant invention because the presently claimed sequence defines a coding single nucleotide polymorphism. Appellant claims that naturally occurring genetic polymorphisms such as that described in the present specification are both the basis of and critical to forensic genetic analysis intended to resolve issues of identity or paternity. Appellant's arguments have been fully considered but are not found to be persuasive because single nucleotide polymorphisms (SNPs) are the most abundant variations in the human genome. Contrary to Appellant's

assertion, a claim to a polynucleotide whose use is disclosed as a marker (for identity or paternity) would not be considered to be specific in the absence of a disclosure of a specific DNA target. A specific utility is a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. **Appellant has not disclosed how this particular SNP has utility from any other SNP** (Emphasis added). Appellant states that until a polymorphic marker is actually described, it cannot be used in forensic analysis. This is not found to be persuasive because a specific utility amounts to more than a starting point for further research and investigation. It does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be.

At the top of page 7 to the middle of page 9 of the Brief, Appellant summarizes case law on the utility requirement. Citing case law, Appellant urges that the present claims clearly meet the requirement of 35 U.S.C. 101. Appellant states that the requirement for a specific utility, which is the proper standard for utility under 35 USC 101, should not be confused with the requirement for a unique utility, which is clearly an improper standard.

Appellant's arguments have been fully considered but are not found to be persuasive. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility. The Examiner is not confusing the standards for utility under 35 USC 101. Furthermore, there is no dispute on the case law itself. The issue at dispute is what constitutes a specific utility. A specific utility is a utility specific to the subject matter claimed. This

contrasts with a general utility that would be applicable to the broad class of the invention. To satisfy the utility requirement under 35 U.S.C. 101, a utility does not need to be unique; *however*, it must be specific. For instance, the instant invention would have a specific utility if it were to show how to diagnose an individual with something specific such as prostate cancer. This utility is specific to the subject matter claimed. The utility is not unique because there are other ways of diagnosing individuals with prostate cancer.

Furthermore, the FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, and the requirement for the utility of the claimed invention is different from the FDA standard for drug approval, 35 U.S.C. 101 does require a specific, substantial, and credible utility, or well-established utility for an invention. Such a utility has to be a "real world " context of use, which does not require significant further research. Appellant confuses this requirement with the "further research and development" needed in pharmaceutical composition and drug development. In other words, a patentable utility has to be **clearly identified or immediately apparent in the specification,** whereas some "further research and development" is permitted in drug development (Emphasis added). For example, determining optimal dosages or drug tolerance in human is further research and development, which is acceptable under 35 USC 101 because it is not significant. On the other hand, determining a specific disease to be treated by a drug constitutes significant further research and development, which is not acceptable under 35 U.S.C. 101.

The instant specification fails to disclose the biological functions, physiological significance, or any specific and substantial utility of the claimed molecules. Without such information, how can one in the skilled art use the claimed invention in a meaningful manner? See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

At the bottom of page 9 to the top of page 10 of the Brief, Appellant asserts that the specification as originally filed, states that the presently claimed sequence encodes a member of the platelet growth factor (PDGF) family. Appellant asserts that this is supported by the fact that four sequences sharing 100% identity at the protein level over an extended region of the claimed sequence are present in the leading scientific repository for biological sequence data and have been annotated by third party scientists who are unaffiliated with Appellants, as homo sapiens platelet derived growth factor C. Appellant cites Exhibits A-C. Appellant states that copies of the abstract, alignment and GenBank reports were provided with the response to the First Office Action and the response to the Final Office Action. At the bottom of page 10 of the Brief, Appellant states that the Examiner questioned the assertion of utility in the Final Office Action. Appellant argues that the Examiner stated that the polypeptide taught by the specification will not have activity as taught by Li *et al.* Appellant argues that the alignments in Exhibits A, B and C were provided to illustrate the extensive homology between the presently claimed sequence and a variety of

members of the platelet derived growth factor family, not to show identity to any one specific members of the platelet derived growth factor family. Appellant argues that evidence of record has been provided that conclusively establishes that those skilled in the art would believe that the specifically claimed sequences encode a member of the platelet growth factor family. Appellant asserts that the Examiner has provided no evidence that directly establishes that the specifically claimed sequence does not encode a member of the platelet derived growth factor family.

Appellant's arguments have been fully considered but are not deemed persuasive. The claimed protein has 305 amino acids (SEQ ID NO:7). The protein of Li *et al.* has 345 amino acids. The sequence alignment demonstrates 100% sequence identity from 1 to 234 amino acid residues. Li *et al.* teach the core region of PDGF-C as amino acid residues 230 to 345. The core region contains the PDGF/VEGF domain. This domain is commonly found in other platelet growth factor family members. Based on the experiments of Li *et al.*, it was demonstrated that the activity of PDGF-C protein is in the core domain (residues 230-345). However, the instant specification teaches that only amino acid residues 1 to 234 share 100% sequence identity with the PDGF-C protein of Li *et al.* Appellant does not demonstrate 100% sequence identity between the instant invention and the PDGF/VEGF domain of Li *et al.* The Exhibits submitted by Appellant fail to demonstrate homology between the critical domains of any platelet growth factor family member. The evidence presented fails to establish

that the claimed sequence encodes a member of the platelet growth factor family.

At the top of page 11 of the Brief, Appellant argues against the applicability of the references cited by the Examiner. Appellant states that the Skolnick reference concerns prediction of function based on the presence of certain functional motifs present within a give protein sequence. Appellant states that the Tischer reference hardly represents the view of those skilled in the art at the time of the present application regarding the prediction of protein function based on homology. Appellant contends that those skilled in the art in 1999 would believe that the claimed sequence is a platelet derived growth factor. Regarding Yan *et al.*, Appellant states that the different receptors bound by the two isoforms are in fact related and the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely of sequence similarity.

Appellant's arguments have been fully considered but are not deemed persuasive. The instant specification teaches that the claimed protein shares structural similarity with animal proteins that contain CUB domains. Thus predictions of function for the instant invention were also made based on the presence of certain functional motifs or structures. The age of the Tischer reference does not take away from the fact that there are circumstances where individual members of a protein family can have distinct and sometimes opposite, biological activities. The Yan *et al.* reference was cited to demonstrate that EDA-A1 and EDA-2, while being members of the tumor necrosis factor family, are

differentially expressed, bind different receptors and may have distinct roles in development of the hair follicle (i.e. two sequences sharing certain degree homology do not necessarily have the same functions).

At the top of page 12 of the Brief, Appellant argues that the PTO has repeatedly attempted to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. Appellant argues that the lack of 100% consensus on prediction of protein function from homology information is completely irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility and that 100% accuracy of prediction of protein function from homology information is not the standard for patentability under 35 USC 101. Appellant argues that the overwhelming majority of those skilled in the relevant art would believe prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools. At the bottom of page 12 of the Brief, Appellant states that the PTO does not require 100% identity between proteins to establish functional homology. Appellant states that Example 10 in the PTO's Revised Interim Utility Guidelines Training Materials only requires a similarity score greater than 95% to establish functional homology.

Appellant's arguments have been fully considered but are not deemed persuasive. The instant specification fails to teach that the present nucleic acid encodes a protein with defined biological functions. The annotations for the

published sequence in Genbank are based upon sequence homology and there is no sufficient information which defines unambigously the functions of the published sequences. The art teaches that it is impossible to predict precisely the functions of protein molecules solely base upon sequence analysis. While sequence analysis is important, the information provided or "predicted" based upon sequence homology can only be used as guidance in determining functions or activities of a molecule by experiments. Any functions predicted based upon the sequence homology will have to be confirmed ultimately by direct experimentation. Appellant is mischaracterizing the Examiner's position regarding the utility of the claimed sequence. A specification can meet the legal requirements of utility and enablement for a nucleic acid as long as the specification discloses a specific and substantial asserted utility or a well-established utility for the claimed nucleic acids. The Examiner stated in the previous Office Action (06 November 2002) that the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product, if the claimed DNA had a specific and substantial utility such as it hybridizes near a disease-associated gene or it has a gene regulating activity. For example, a hypothetical specification discloses that a claimed nucleic acid is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the nucleic acid. The claimed nucleic acid in the hypothetical example would not be rejected under 35 U.S.C. 101 and 112, first paragraph, as it has a specific and substantial and is enabled as a colon cancer marker. The instant

specification, however, failed to disclose that the DNA of the instant application could be linked to a specific disease or gene regulating activity. There is no disclosure that the claimed nucleic acids are expressed at altered levels or forms in any specific, diseased tissue. No evidence has been brought forth during the prosecution history regarding the specific biological functions or physiological significance of the proteins encoded by the claimed nucleic acid sequences. It clearly weighs in favorite of the Examiner's position that the functions of the proteins encoded by the claimed nucleic acid sequences remain elusive. In Example 10 of the Revised interim Utility Guidelines Training Materials, the claimed nucleic acid sequence has a well-established utility because the high sequence homology can place the protein encoded by the claimed nucleic acid sequence in a DNA ligase family, whereas ligases have a well-established use in ligating DNA. It is not the case here.

At the middle of page 13 of the Brief, Appellant states that given the well established biological and medical relevance of platelet derived growth factor proteins; those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the proteins. Appellant states that the specification describes how the sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Appellant maintains that DNA chips clearly have utility as evidenced by hundreds of issued U.S. Patents. Appellant states that the present sequences are specific markers of the human genome and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the

art would instantly recognize that the present nucleotide sequences would be ideal, novel candidates for assessing gene expression using such DNA chips. On page 14 of the Brief, Appellant states that further evidence of the real world substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Appellant states that there are many companies that have at one time or another, concentrated on the use of gene sequences or fragments in gene chip and non-gene chip formats. At the bottom of page 14 of the Brief, Appellant states for the record that the presently claimed sequences have utility in assessing gene expression patterns using such gene chips as those described in the issued U.S. Patents.

Appellant's arguments have been fully considered but are not deemed persuasive for the following reasons. Commercial success is not an indication of patentability and the commercial value does not simply render the claimed invention a specific, substantial, and credible utility. This is because many products may be commercially successful due to reasons unrelated to the use of the products such as fads or clever commercial advertising. For example, a pharmaceutical company may wish to purchase a putative growth factor on the chance that it may turn out to be a drug target in the future, even though determining such possibility requires substantial further experimentation. However, such substantial further experiment is not acceptable for patentable utility.

A gene chip is a customized device in biomedicine that allows researchers to detect, simultaneously, the presence and activity patterns of tens of thousands of DNA sequences in pieces of genetic material. A microarray can be used by researchers to describe the genetic malfunction associated with a disease, detect the presence of the disease in a particular patient, calculate a patient's genetic predisposition to that disease or identify the medicines likely to be most effective in treating a particular patient with the disease. The instant specification has not established that the claimed nucleic acid sequences are expressed at altered levels or forms in a specific diseased tissue as compared with the corresponding healthy tissue. If the claimed nucleic acid molecules were in a microarray and a compound caused decreased expression of the claimed nucleic acids, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate an unspecified disease? If it had been disclosed that the claimed nucleic acids are expressed at a higher level in a particular diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the nucleic acid molecules is a good drug candidate that targets the disease. It is not the case here. In addition, the claimed nucleic acid molecules may very well be expressed at equivalent levels in healthy tissues. If that were the case, then the compound would not be a good drug candidate. The claimed nucleic acid molecules may also very well be expressed at a lower level in a particular diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed

polynucleotides would not be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed nucleic acid molecule as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed nucleic acid molecules (or proteins encoded by the nucleic acids) and any diseases or disorders, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696. Thus, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Finally, the issued U.S. Patents related to DNA chips demonstrate that the technology itself is important and useful; they do not show that claimed invention has a patentable utility. There is no doubt that a gene chip (or DNA chips) is a valuable tool in gene expression monitoring and drug discovery. As was stated by Appellant, the instant claims are not drawn to the technique, rather to nucleic acid molecules. However, the nucleic acid molecules have not been disclosed as being associated with any particular diseases or conditions by its being expressed at an altered level or form in a specific diseased tissue as compared to the corresponding healthy tissue. **Any such nucleic acid molecules could be added to a microarray** (Emphasis added). The use of the claimed uncharacterized nucleic acid molecules in such studies would have provided no more valuable information than the use of any other unidentified nucleic acids. Thus, this asserted utility is not specific. Determining the relationship between

the claimed nucleic acid molecules and any specific diseases or disorders would require significant further research. Therefore, this asserted utility is also not substantial.

In the middle of page 15 of the Brief, Appellant states that the present nucleotide sequences have a specific utility in determining the genomic structure, for example in the identification of coding sequence and mapping the gene to a particular chromosome. Appellant maintains that this is evidenced by the fact that SEQ ID NO:6 can be used to map the 5 coding exons on chromosome 4. Appellant cites Exhibit J. Appellant states that only a minor percentage of the genome actually encodes exons, which in turn encode animo acid sequences. Appellant argues that the claimed polynucleotide sequences have utility in "identification of exon splice junctions" and provide biologically validated empirical data that specifically define that portion of the corresponding genomic locus that actually encodes exon sequence. At the bottom of page 16 of the Brief, Appellant points out that only those small percentage of nucleotide sequences that are located in this region of chromosome 4 can be used in such a manner and not just any polynucleotide. Appellant argues that the Examiner is confusing the requirements of a specific utility with a unique utility. At the top of page 17 of the Brief, Appellant states that the question of whether or not other nucleic acid sequences can be used to assess gene expression using DNA chips is completely irrelevant to the present utility inquiry. Appellant maintains that the only relevant question in regard to meeting the standards of 35 USC 101 is whether every nucleic acid can be so used.

Appellant's arguments have been fully considered but not deemed persuasive because such a utility is considered a research utility only designed to identify a particular function of the claimed sequences and is not a substantial utility. See, e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." The use of the polynucleotide sequences in gene mapping does not represent a specific and substantial utility. Appellant demonstrates the significance of expressed sequences in the structural analysis of genomic data; but fails to show that the present polynucleotide sequences have a patentable utility. As was previously stated, to satisfy the utility requirement under 35 U.S.C. 101, a utility does not need to be unique; however, it must be specific. The use of the present nucleic acid in tracking gene expression patterns on a gene chip is not specific, because such a use would be applicable any to nucleic acids. Appellant fails to specifically disclose the use of the present nucleic acid sequences in mapping the protein coding regions (5 coding exons of the gene encoding SEQ ID NO:7) in chromosome 4 in the specification as originally filed. Furthermore, many polynucleotides are known in the art to encode polypeptides, yet the polypeptides have no known function.

Beginning at the middle of page 17 of the Brief, Appellant summarizes case law on the utility requirement. Citing case law, Appellant urges that the present claims clearly meet the requirement of 35 U.S.C. 101. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility. At the bottom of page 17 to the middle of page 18

of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines and the validity of issued US patents. It is noted that an Examiner has no authority to comment on the legality of the Guidelines and the validity of US Patents.

Appellant's arguments have been fully considered but are not deemed persuasive. The statement, "(t)o violate 101 the claimed device must be totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), indicates that a rejection under 35 U.S.C. § 101 for lack of operability can be overcome by a showing of actual use or commercial success. The claimed invention in the instant case is drawn to nucleic acid sequences, not a device; the instant rejection under 35 U.S.C. 101 is not directed to inoperativeness of a device, rather to a lack of patentable utility of the claimed nucleic acid sequences; and the instant issue is whether the asserted utilities meet the three-pronged test for a patentable utility. Since the specification fails to disclose a specific, substantial utility or a well-established utility, the present claims do not satisfy the utility requirement of 35 U.S.C. 101. Merely citing case laws on the utility requirement does not render a patentable utility for the present invention. While "anything under the sun that is made by man" is patentable, it does not necessarily mean the present invention is patentable. In fact, the present invention is not patentable due to lack of a patentable utility.

On page 18 of the Brief, Appellant concludes this section by urging that the rejection of claims 4-11 under 35 U.S.C. 101 must be overruled. The

Examiner believes that the rejections should be sustained for the reasons set forth above.

B. Are Claims 4-11 Unusable Due to a lack of Patentable Utility?

As Appellant indicates at the bottom of page 18 of the Brief, claims 4-11 are not enabled due to lack of patentable utility under U.S.C. 101 for the reasons set forth above. A rejection under U.S.C. 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 35 U.S.C. 101.

Appellant incorporates their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Appellant's arguments and exhibits have been fully and carefully considered, but are not found to persuasive for the reasons discussed above in the maintained rejection in 35 USC 101. The Examiner believes that the rejections should be sustained.

C. Are Claims 4, 7 and 8 Enabled?

The Examiner would like to clarify that claims 4-11 are properly rejected under 35 U.S.C. 112, first paragraph, enablement, due to lack of a patentable utility under U.S.C. 101 for the reasons set forth above.

Furthermore, even if the nucleic acid molecule of SEQ ID NO:6 or encoding the amino acid sequence set forth in SEQ ID NO:7 (claims 4-11) were to have a patentable utility, the instant disclosure would not be found to be enabling for claims 4, 7 and 8. The specification is not enabling for polynucleotide comprising fragments. The claimed invention comprises a genus

of at least 24 contiguous nucleotides of SEQ ID NO:6, as recited in claim 4. Claims 7 and 8 depend from claim 4.

Beginning at the middle of page of 19 of the Brief, Appellant states that there is no requirement that all species of an invention must have all of the exact properties. Appellant argues that the Examiner requires the polynucleotide fragments to have the same structure and activity as the length protein encoded by SEQ ID NO:6. Appellant states that the Examiner believes that the only desirable property that a polynucleotide fragment of the present invention could have is the specific biological properties of the full length protein encoded by SEQ ID NO:6. At the middle of page 20 of the Brief, Appellant argues that significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling to chromosomal mapping are practiced utilizing nucleic acid sequences and techniques that are well known to those of skill in the art. Appellant further submits that the skilled artisan can clearly make and use the claimed polynucleotides, which is all that is required to meet the enablement requirement under 35 U.S.C. 112, first paragraph. Appellant further submits, citing case law, that it is well established that the enablement requirement is met if any use of the invention (or in this case, certain species of the invention) is provided.

Appellant's arguments have been fully considered but are not deemed persuasive. The enablement issue is judged against the well-established Wands factors, as recited in the office action. The key issue here is the breadth of the

claims. Claim 4 is drawn to an isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6. Thus, the claim recites a genus of nucleic acid molecules of any size comprising at least 22 contiguous nucleotides of SEQ ID NO:6. While some of species of the genus may retain a readily apparent use **if such a use were present for the full-length molecule**, the instant disclosure would not be found to be enabling for the whole genus because the instant disclosure fails to show (i) which portions of SEQ ID NO:6 are critical to the activity of the protein of SEQ ID NO:7; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO:6 will result in protein mutants with the same functions as the protein of SEQ ID NO:7.

While there is no requirement for all species of a genus to have exactly same properties, the disclosure has to enable an artisan to make and use the genus. Appellant's argument that the enablement requirement is met if any use of the invention (or in this case, certain species of the invention) is provided is incorrect. To satisfy the enablement requirement, the disclosure must teach how to make and use the invention. Merely providing asserted uses does not satisfy the enablement requirement under 35 U.S.C. 112, first paragraph. In the instant case, the disclosure must teach an artisan how to make and use the whole genus, not just the full length nucleic acid sequence of SEQ ID NO:6, which encodes an amino acid sequence of SEQ ID NO:7 because the majority of the species of the genus do not obviously encode SEQ ID NO:7.

At page 21 of the Brief, Appellant argues against the Examiner's position that, "in the absence of specific hybridization language, the polynucleotide fragments may correspond to any region that is highly conserved in a gene family" and that "it allows imperfect matches and carry the risk of obtaining false signals from unrelated DNA sequences". Appellant argues that claims 4, 7 and 8 do not concern hybridization at all and that the claims requires at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP gene described in SEQ ID NO:6. Appellant states that the Examiner's conclusion that the polynucleotide fragment may correspond to any region that is highly conserved in a gene family is unfounded because there are no art rejections against polynucleotide fragments comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6.

Appellant's arguments have been fully considered but are not deemed persuasive. Appellant argued in the previous Office Action that the genus of nucleic acid molecules could be used for primers or probes. The Examiner stated that the instant disclosure failed to provide information or sufficient guidance on how to make and use the claimed genus due to the unpredictable nature of nucleic acid hybridization and the possibility that a claimed nucleic acid molecule may hybridize to a nucleic acid other than the portion of SEQ ID NO:6. In addition, fragments of polynucleotides often have less specificity than the full length sequence and thus would allow for imperfect matches. Lastly, rejections of claims under 35 U.S.C. 112, first paragraph and 35 U.S.C. 102/103 are considered separately. Thus, the rejection of the instant claims under 35 U.S.C.

§112, first paragraph, does not contradict the fact that the claims are free of the prior art.

At the bottom of page 21 of the Brief, Appellant argues that there is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention without further details in a patent specification. Appellant maintains that one skilled in the art can used the disclosed sequence to design oligonucleotide probes and primers and use them in PCR based screening and detection methods to obtain the described sequences and/or determine tissue expression patterns. Appellant states that the present specification provides highly detailed descriptions of techniques that can be used to accomplish many different aspects of the claimed invention, including recombinant expression, site-specific mutagenesis, *in situ* hybridization, and large scale nucleic acid screening techniques. Appellant states that the specification properly incorporates by reference a montage of standard texts in the specification to provide even further guidance to the skilled artisan. Appellant argue that an alleged lack of expressed teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform techniques required to perform at least one aspect of the invention. Appellant states that as a matter of law, it is well settled that a patent need not disclose what is well know in the art.

Appellant's argument has been fully considered but is not deemed persuasive because while standard molecular biological techniques are routine in the art, the general teachings in the art **are not directed to the specific genus**

of the nucleic acids of the present invention (SEQ ID NO:6) and do not provide sufficient guidance on how to make and use the claimed genus of nucleic acid molecules (Emphasis added). The skilled artisan would not be able to use the claimed broad genus to specifically determine, for example, the expression of the claimed nucleic acid in a tissue, due to the unpredictable nature of nucleic acid hybridization and the possibility that a claimed nucleic acid molecule may hybridize to a nucleic acid other than the portion of SEQ ID NO:6. The state of the art is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches is unpredictable. Thus, neither the specification nor the art provides sufficient teachings on how to make and use the claimed genus.

Beginning at bottom of page 22 to the middle of page 23 of the Brief, Appellant argues that the Examiner has stated that the specification provides insufficient guidance regarding the biological functions or activity of certain of the claimed compositions. Appellant submits that such an enablement standard conflicts with established patent law. Appellant further argues that a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art.

Appellant's argument has been fully considered but is not deemed to be persuasive for the following reasons. Without disclosure of the relation of the function to structure of SEQ ID NO:7, one skilled in the art would not be able to make and use an isolated nucleic acid molecule comprising at least 22 contiguous bases of SEQ ID NO:6, which has 918 nucleotides and encodes a

protein with 305 amino acids. Without disclosing portions of SEQ ID NO:6 which are critical to the activity of the protein of SEQ ID NO:7, an artisan would have to perform undue experimentation to find out those species that encode a functional protein. A skilled artisan would not be expected to make and use the claimed genus of nucleic acids, which comprises an enormous number of inoperative species, without undue experimentation.

At the middle of page 23 of the Brief, Appellant argues, citing case law, that a specification "need describe the invention only in such detail as to enable a person skilled in the art in the most relevant art to make and use it." Appellant submits that the specification details numerous applications in which claimed nucleotide sequences can be used, for example, to track gene expression using gene chips. Appellant further submits that since public domain nucleotide sequences that have not been associated with any particular biological function, let alone validated as coding sequences, are used everyday in gene chip applications, it defies logic that undue experimentation would be required to use the presently described nucleotide sequences, which have been biologically validated as coding sequences, in the very same gene chip applications.

The Examiner agrees that a specification needs to describe an invention only in such detail as to enable an artisan to make and use it. However, the instant specification fails to describe the claimed invention in such detail as to enable an artisan to make and use the claimed genus of nucleic acids for the reasons set forth above. Furthermore, Appellant's argument fails to address the enablement rejection, i.e., how to make and use the genus of nucleic acids. As

noted above, while some of species of the genus may retain a readily apparent use if such a use were present for the full-length molecule, the specification would not be found to be enabling for the whole genus.

Appellant concludes this section by urging that the rejection of claims 4, 7 and 8 under 35 U.S.C. 112, first paragraph must be overruled. The Examiner believes that the rejections should be sustained for the reasons set forth above.

D. Does claim 4 lack sufficient Written Description?

At page 24 of the Brief, Appellant argues, citing case law, that an "Appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention". Appellant states more case law; "although the Appellant does not have to describe exactly the subject claimed the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". At the bottom of page 24 of the Brief, Appellant argues that the Examiner stated that claim 4 fails to meet the written description requirement because the specification discloses only a structural feature. Appellant submits that this is all that is required for claim 4 to meet the written description of 35 U.S.C. § 112, first paragraph.

Appellant's arguments have been fully considered but are not deemed persuasive. The instant claim encompasses virtually any random sequence of any length as long as it has a stretch of at least 24 consecutive nucleotides of SEQ ID NO:6. The claim does not require that the nucleic acid molecules possess any particular biological activity, nor any particular conserved structure,

or other disclosed distinguishing feature. SEQ ID NO:6 consists of 918 nucleotides, thus there are enormous combinations of "at least 24 consecutive nucleotides of SEQ ID NO:6", which cover different regions of SEQ ID NO:6. Consequently, the limitation "at least 24 consecutive nucleotides of SEQ ID NO:6" does not define conserved structure. There is no definitive function linked to such a limitation "at least 24 consecutive nucleotides of SEQ ID NO:6". Thus, only an isolated nucleic acid molecule comprising SEQ ID NO:6, but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph.

At the top of page 25 of the Brief, Appellant summarizes the description requirement by citing case law. Appellant argues that the nucleic acid sequence of the present invention are distinguished by structural features—a chemical formula, *i.e.,* the sequence itself. The skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. On page 26 of the Brief, Appellant argues that as there are no art rejections against polynucleotide fragments comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6, the conclusion reached by the Examiner in no way satisfies the Examiner's burden of establishing a prima facie case that claim 4 lacks sufficient written description support, let alone serves to overcome the controlling legal precedent that allows the skilled artisan to distinguish the claimed nucleic acids from other materials.

Appellant's arguments have been fully considered but are not deemed persuasive for the following reasons. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of partial structure: comprising at least 24 contiguous nucleotides of SEQ ID NO:6. There is not even identification of any particular portion of the structure that must be conserved. It is further noted that "comprising at least 24 contiguous nucleotides of SEQ ID NO:6" is only a partial structure of the genus. It is not a chemical formula because a chemical formula would accurately define the composition of a molecule. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Only an isolated nucleic acid molecule comprising SEQ ID NO:6, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Lastly in response to Appellant's repeated assertion that, "there are no art rejections against polynucleotide fragments comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6, rejections of claims under

35 U.S.C. 112, first paragraph and 35 U.S.C. 102/103 are considered separately. The rejection of claim 4 under 35 U.S.C. §112, first paragraph, does not contradict the fact that the claim is free of the prior art.

Appellant concludes this section by urging that the rejection of claim 4 under 35 U.S.C. § 112, first paragraph must be overruled. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Respectfully submitted,

RMD
May 12, 2004

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conferees
Gary Kunz, Ph.D.
SPE, Art Unit 1647

Yvonne Eyler, Ph.D
SPE, Art Unit 1646

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600